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10/674,387	10/01/2003	Yoshihide Iwaki	2870-0266P	4434

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EXAMINER
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KAPUSHOC, STEPHEN THOMAS

ART UNIT	PAPER NUMBER
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1634

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/28/2007	ELECTRONIC

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<b>Office Action Summary</b>	<b>Application No.</b> 10/674,387	<b>Applicant(s)</b> IWAKI ET AL.	
	<b>Examiner</b> Stephen Kapushoc	<b>Art Unit</b> 1634	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 October 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 2-26 is/are pending in the application.
- 4a) Of the above claim(s) 12-24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-11, 25, 26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

Claims 2-26 are pending.

Claim 1 is cancelled.

Claims 12-24 are withdrawn.

Claims 2-11, 25, and 26 are examined on the merits.

#### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/26/2006 has been entered.

This Office Action is in reply to Applicants' correspondence of 10/26/2006. Claim(s) 1 is/are cancelled; claim(s) 12-24 is/are withdrawn; claim(s) 25 and 26 has/have been newly added; claim(s) 2-6, 8, and 11 has/have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

#### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26 is unclear over the recitation of the phrase 'mismatch nucleotide in said second nucleotide is cytosine', where the phrase 'mismatch nucleotide in said second primer is cytosine' is more clear because there is no antecedent basis for any 'second nucleotide' in either claim 26, or claim 25 (from which claim 26 depends).

***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 2, 5, 6, 7, 11 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Ye et al (2001).

Ye et al teaches methods for detecting single nucleotide polymorphisms comprising designing allele specific primers wherein each primer has a different artificial mismatch nucleotide, and amplifying a sample with the primers. Ye et al shows that the amount of an amplification product from each primer is substantially the same when both alleles are present in the sample.

Regarding claim 25 (claim 25 is the independent claim, and thus discussed first in this rejection), Ye et al teaches designing two allele specific primers (Fig 1; and for

example Table 2 -TNF -308G→A primers for A and G alleles). Specifically, Ye et al teaches a first primer (Table 2 Forward inner primer (A allele)) that contains an artificial mismatch (see Table 1, Tetra-primer ARMS-PCR primers have an additional mismatch at position -2 from the 3' terminus) and a nucleotide complementary to a first allele (see Table 1, Tetra-primer ARMS-PCR primers have an allele-specific mismatch at the 3' terminus). Ye et al further teaches a second primer (Table 2 Reverse inner primer (G allele)) that contains an artificial mismatch (see Table 1, Tetra-primer ARMS-PCR primers have an additional mismatch at position -2 from the 3' terminus) and a nucleotide complementary to a second allele (see Table 1, Tetra-primer ARMS-PCR primers have an allele-specific mismatch at the 3' terminus). As such the two primers can distinguish between the two alleles. The artificial mismatch nucleotides in the first and second primers are different (G and A in the first and second primers, respectively). Ye et al further teaches amplifying a sample with the recited primers (p.3 – Tetra-primer ARMS-PCR) and shows that the amount of amplification product from each primer is substantially the same in a heterozygous sample, where both alleles are present in the sample (Fig 2A, top picture, lane 2 for example).

Regarding claim 2, Ye et al teaches that the Allele-specific mismatch is at the 3'-terminal base (Table 1), thus the primers have a polymorphic site within 4 nucleotides from the 3'terminus of the allele-specific primers.

Regarding claims 5, 6, and 7, Ye et al teaches detection using polymerase reactions (p.6 – Results of tetra-primer ARMS-PCR), relevant to claim 5, and teaches

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detection of the PCR product, relevant to claim 6, via gel electrophoresis, relevant to claim 7 (p.3, right col., last ¶).

Regarding claim 11, Ye et al teaches determining the presence of each allele, thus determining the homo/heterozygosity of the SNP (Fig 2).

6. Claims 2-7, 11 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrie et al (1992).

Ferrie et al teaches a method for the analysis of mutations in the CFTR gene, including single nucleotide polymorphisms. Ferrie et al teaches designing and allele specific primers wherein each primer has a different artificial mismatch nucleotide (Table 4 - 621 +1G>T), and amplifying a sample with the primers. Ferrie et al shows that the amount of an amplification product from each primer is substantially the same when both alleles are present in the sample.

Regarding claim 25 (claim 25 is the independent claim, and thus discussed first in this rejection), Ferrie et al teaches designing two allele specific primers (Table 3 – ΔF508 primers DF-j-N and DF-w-M; Fig 1). It is noted that while the F508 mutation is fully described as a deletion of 3 nucleotides, the primers of Ferrie et al can be considered as detecting a single nucleotide polymorphism (i.e. the primers detect whether the nucleotide prior to the sequence context TTGGTGTT (in Fig 1 a)) is either a 'T' (normal sequence) or an 'A' (F508 sequence). Specifically, Ferrie et al teaches a first primer (Table 3 DF-j-N primer) that contains an artificial mismatch (see Figure 1 a) and a nucleotide complementary to a first allele (the primer has a 3'-terminal A

complementary to the 'normal' allele). Ferrie et al further teaches a second primer (Table 3 DF-w-M primer) that contains an artificial mismatch and a nucleotide complementary to a second allele (the primer has a 3'-terminal T complementary to the 'F508' allele). As such the two primers can distinguish between the two alleles. The artificial mismatch nucleotides in the first and second primers are different (C and T in the first and second primers, respectively). Ye et al further teaches amplifying a sample with the recited primers (Figure 1a)) and shows that the amount of amplification product from each primer is substantially the same in a heterozygous sample, where both alleles are present in the sample (Fig 1a), gel picture, lanes in sample 4 for example).

Regarding claim 2, Ferrie et al teaches primers in which the allele-specific mismatch is at the 3'-terminal base (Figure 1a)), thus the primers have a polymorphic site within 4 nucleotides from the 3'terminus of the allele-specific primers.

Regarding claims 3 and 4, the reference teaches that the artificial mismatch nucleotide is adjacent to the allele-specific nucleotide in each primer (Fig 1a)), thus teaching that the mismatch nucleotide is introduced to the nucleotide adjacent to the polymorphic site in at least one (relevant to claim 3) and both (relevant to claim 3) primers.

Regarding claims 5, 6, and 7, Ferrie et al teaches detection using polymerase reactions, relevant to claim 5, and teaches detection of the PCR product, relevant to claim 6, via gel electrophoresis, relevant to claim 7 (p.252 – ARMS reaction conditions).

Regarding claim 11, Ferrie et al teaches determining the presence of each allele, thus determining the homo/heterozygosity of the polymorphic position (Fig 1a) teaches

analysis of normal samples (homozygous for no F508 deletion) and  $\Delta$ F508 heterozygous sample).

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ye et al (2001) US in view of Durward et al (1998).

Regarding claim 25, upon which claims 8 and 9 are dependent, Ye et al teaches methods for detecting single nucleotide polymorphisms comprising designing allele specific primers wherein each primer has a different artificial mismatch nucleotide, and amplifying a sample with the primers. Ye et al shows that the amount of an amplification product from each primer is substantially the same when both alleles are present in the sample. Ye et al teaches all of the limitations required of claim 25.

Ye et al does not teach the analysis of a PCR by-product that is pyrophosphoric acid (PPi) for detection.

Durward et al teaches a colorimetric method for detecting amplified nucleic acids based on measuring PPi (p.608, right col., lns.23-28). The reference teaches that during the PCR reaction the incorporation of dNMPs from dNTPs into amplified nucleic

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acids generates inorganic pyrophosphate (PPi, phosphoric acid) in a predicable 1:1 molar ratio (p.608, right col., Ins.18-28; Fig.1). The reference further teaches that PPi can be hydrolyzed to inorganic phosphate (Pi) (p.608, right col., Ins.31-32), that detection and measurement of Pi is a measure of PCR performance (p.608, right col., Ins.33-36), and describe an assay for Pi measurement (p.608, right col., Ins.41-52). Durward also provides examples in which amplified DNA is detected by Pi measurement (Fig.2; Fig.3; Table 1). Because the Pi results directly from the hydrolysis of PPi, this measuring technique is using the PPi.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined the allele specific amplification methods of Ye et al with the phosphate measurement detection methods of Durward et al. One would have been motivated to do so based on the assertion of Durward et al that PCR measurement by phosphate detection can offer advantages in terms of speed and low cost (p.610, left col., Ins.35-36). One would have had a reasonable expectation of success because Durward et al provides examples of sensitive and specific detection of PCR performance using the method (Fig.2; Fig.3).

Therefore, in view of the prior art, the claimed invention is prima facie obvious.

8. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ye et al (2001) in view of Durward et al (1998) as applied to claims 8 and 9 above, and further in view of Fujisaki et al (1999) US Patent 5,935,520.

The teachings of Ye et al in view of Durward et al are applied to claim 10 as they are applied to the rejection of claims 8 and 9 previously in this office action.

Durward et al teaches detection of PCR performance by measuring the optical density of phosphomolybdenum complex reduced by Fiske-Subbarow reagent.

Ye et al in view of Durward et al does not teach the use of a dry analytical element for the analysis of production of the PCR product.

Fujisaki et al teaches a dry analytical element for analyzing an analyte in a sample solution using a colorimetric reaction (col.1. Ins.39-50). The reference teaches the use of a reagent layer in the element that contains components necessary for producing a colorimetric reaction.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the methods of Ye et al in view of Durward et al to have included the dry analytical element taught by Fujisaki et al for the measurement of PCR performance. One would have been motivated to do so based upon the assertion of Fujisaki et al that such dry analytical elements provide for the simple and rapid analysis of sample solutions (col.1 Ins.32-37). One would have had a reasonable expectation of success because Fujisaki et al teaches that dry analytical elements can utilize color reaction based assays (col. 1 Ins.45-50) in which components necessary for the coloring reaction are contained in a reagent layer (col 8 Ins.45-47), and Durward et al demonstrate that the reagents used to create the color change (molybdate and Fiske-Subbadow solution) to measure PCR performance are added sequentially to the PCR mix for the assay (p.609, middle col., Ins.10-18).

Therefore, in view of the prior art, the claimed invention is prima facie obvious.

7. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ye et al (2001).

Ye et al teaches methods for detecting single nucleotide polymorphisms comprising designing allele specific primers wherein each primer has a different artificial mismatch nucleotide, and amplifying a sample with the primers. Ye et al shows that the amount of an amplification product from each primer is substantially the same when both alleles are present in the sample. Ye et al teaches all of the limitations required of claim 25, from which claim 26 depends.

Ye et al does not provide primers in which the two different mismatched nucleotides are adenine in a first primer and cytosine in a second primer.

However, Ye does teach a rationale for providing a mismatched nucleotide in a primer (p.2, right col., Ins.3-11). Ye et al teaches that different mismatches can be either 'strong' (G/A or C/T mismatches), 'weak' (C/A or G/T mismatches), or 'medium' (A/A, C/C, G/G, or T/T mismatches), and that one can pair the mismatches within a primer to achieve the desired level of selectivity.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the general method taught by Ye et al so as to have used any mismatched nucleotides, including an adenine in a first primer and a cytosine in a second primer, that would provide the desired level of amplification selectivity for each primer. Such experimentation to provide different oligonucleotide

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primers with different artificial mismatches would be routine to one of skill in the art at the time the invention was made, as evidenced by the teachings and examples of Ye et al.

Thus, in view of the teachings of Ye et al, the claimed invention is prima facie obvious.

### ***Response to Remarks***

Applicants remarks of 10/26/2006 are drawn to the deficiencies of the previously cited reference of Newton et al (1997) US Patent 5,595,890. In light of the amendments to the claims, new grounds of rejection, which do not include the teachings of Newton et al, have been applied. As such, the Remarks drawn to the previous rejections are moot in light of the newly presented rejections set forth in this Office Action.

### ***Conclusion***

No claim is allowable. No claim is free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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